

MONITORING FLUID SHIFTS DURING HAEMODIALYSIS (HD) USING ELECTRICAL BIOIMPEDANCE TECHNIQUES

Omar.I.Al-Surkhi¹, P.J. Riu¹, F.Bogonez¹, F. Vazquez¹, J. Ibeas. MD²

¹ Biomedical Engineering Research Center (CREB), Technical University of Catalonia UPC, Barcelona Spain

²Department of Nephrology, Parc Taulí Medical Centre, Sabadell, Spain

e-mail: omar@eel.upc.edu

Abstract-Haemodialysis has been considered an effective therapy for patients with end-state renal disease; however, patients can suffer from adverse side effects during haemodialysis. About 25% of patients who need haemodialysis treatment experience acute complications (haemodynamic instability) during the treatment sessions, which provoke discomfort in the patients due to hypotension, fainting, vomiting, etc., and usually require relatively long recovery periods. These instabilities are related to the excess shift of fluids between the extracellular (ECW) and intracellular (ICW) spaces as shown in several publications during the past 10 years. In this work we propose a non-invasive method based on local multifrequency bioimpedance measurements that allow us to determine the fluid distribution and variations during haemodialysis. For that purpose a measurement system was developed for the measurement of the body fluid balance changes (ratio ECW/ICW) during haemodialysis sessions. Clinical measurements were done using 10 HD patients during 60 HD sessions. Bioimpedance data, arterial blood pressure, blood volume and blood hematocrit variations were recorded continuously during the HD sessions. Impedance values at infinite and zero (R_{∞}, R_0) frequencies were extrapolated from Cole-Cole mathematical model. These values are assumed to represent the impedance of total tissue fluid and the impedance of the extracellular space respectively. Estimators for the extracellular and intracellular fluid volumes were developed using Hanai theory of mixtures with values of (R_{∞}, R_0). Significant decrease in the ECW volumes were recorded during HD session for all patients, however ICW variations were not similar in all patients. In this phase of the research work, the selected patients were stable; however, in future work non-stable patients will be selected and the electrical impedance measurements of the fluid variations will be used to develop an indicator of hypovolemic crisis during HD thus allowing a better control of the adverse effects during dialysis sessions.

Keywords - Multifrequency Bioimpedance, Haemodialysis, body fluid compartments.

I. INTRODUCTION

Numbers of patients suffering from Chronic Kidney Disease (CKD) are very serious. 20 million Americans (1 in 9 US adults) have CKD and another 20 million more are at increased risk [National Kidney Foundation, 2006]. The progress of kidney disease may lead to kidney failure, which requires dialysis or a kidney transplant to maintain life. Haemodialysis has been considered an effective therapy for patients with end-state renal disease. CKD patients usually suffer from excess of toxic end-products of nitrogen metabolism (urea, creatinine, uric acids, and etc.) accumulated in the blood and tissues. Furthermore, these patients have a defected salt-water balance that will result in shrunken body cell mass with relatively expanded ECW space [Jaeger and Ravindra, 1999]. About 25% of patients who need haemodialysis treatment can suffer from adverse

side effects during haemodialysis such as hypotension, headache and vomiting. Most of these irritating symptoms are related to the excess shift of fluids between the extracellular-ECW- and intracellular spaces - ICW- as shown in several publications during the past 10 years. The applications of bioimpedance techniques in the analysis of body compartments are broad. Hundreds of publications in this field are available in the literature from the last 30 years. Bioimpedance measurements used to evaluate the correlation between the Total Body water (TBW) and electrical impedance were first reported by Hoffer(1969) using a single frequency impedance analysis (BIA) [7] in which he presented the correlation between the total body water(TBW) and total body impedance. Bioimpedance analysis (BIA) was proposed as a method to measure the fat-free mass (FFM) by Lukaski (1985) [8]. The applications of BIA were further extended to measure the extracellular water (ECW) [9] and body cell mass (BCM) [10]. Most Bioimpedance measurements are performed using four electrodes: The current (<1mA) is passed through the 2- injection electrodes, while the voltage drop is measured using the 2-detection electrodes. From the injected current and the measured voltage drop values, the impedance is derived and the total volume can be estimated. Bioimpedance spectroscopy (BIS) combines suspension theories for volume estimation [11] with biophysical model in which a spectrum of frequencies is used to describe resistance and reactance of the whole tissue. The resistance of intracellular (ICW) and extracellular ECW) mediums can be determined and their volumes are estimated using BIS with a range of frequencies (5kHz to 1MHz).

II. THEORY

A. Bioimpedance as a function of frequency

In biological systems cell membranes act like capacitors, thus the injected current at low frequency (LF) will only penetrate the ECW; while at very high frequencies(HF) the current will penetrate both the ECW and ICW.

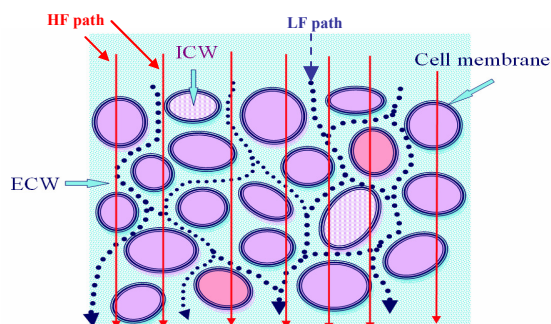


Fig. 1. Electrical current paths in biological tissue at LF and HF.

A useful method for illustrating the behavior of tissue impedance as a function of frequency is done by fitting the

measured bioimpedance with the Cole-Cole mathematical model developed by (Cole and Cole, 1941)[9].

The Cole-Cole model obeys the following equation:

$$Z(\omega) = R_{\infty} + \frac{R_0 - R_{\infty}}{1 + (j\omega\tau_c)^{1-\alpha}} \quad (1)$$

Where:

$Z(\omega)$: impedance as a function of the angular frequency (radians per second)

R_0 : resistance at $\omega = 0$

R_{∞} : resistance at $\omega = \infty$

τ_c : time constant

α ($0 \leq \alpha \leq 1$) is a characteristic parameter of the distribution of the relaxation frequencies of the various structures making up the heterogenous material.

As shown in Eq.1 bioimpedance is complex, therefore it can generally be described as :

Complex: $Z = R + jX$

$$\text{Module: } |Z| = \sqrt{R^2 + X^2} \quad (2)$$

$$\text{Phase: } \phi = \tan^{-1}\left(\frac{X}{R}\right)$$

R and X are the real and imaginary part of the complex bioimpedance. Bioimpedance module, phase, real and imaginary part are usually plotted as a function of frequency domain. Fig.2-4 display the behaviour of the impedance in several forms, at the frequencies of 10 kHz, 20 kHz, 50 kHz, 100 kHz, 220 kHz and 500 kHz.(real data measured from human muscular tissue). Fig.2 shows the real part of the measured data (small circle points) plotted with the fitting Cole-Cole model (solid line) as a function of the frequency. It is important to note that to measure values close to the limiting ones the frequency range would have to be extended at least in two decades.

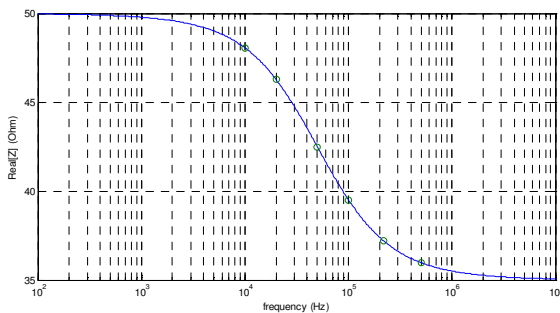


Fig. 2. Real part of bioimpedance as function of frequency.

Fig.3 displays the imaginary part in absolute value because it is negative for biological media

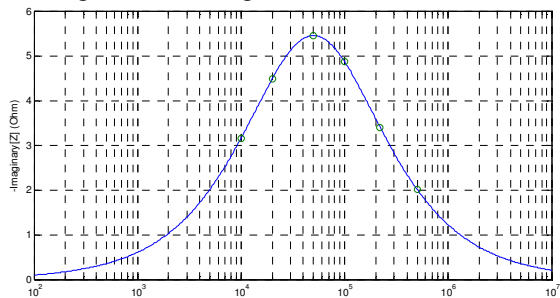


Fig. 3. Imaginary part of bioimpedance as function of frequency.

The phase angle plotted in Fig.4 displays a behaviour similar to the imaginary part. Phase angles are also negative, and in this case quite low. To present to Cole-Cole data in the complex plane, the real component R is plotted versus imaginary component. Fig.5 displays a complex plane diagram, sometimes called the Wessel diagram. A circular arc is obtained. The circular arc corresponds to a half circle only if $\alpha=0$.

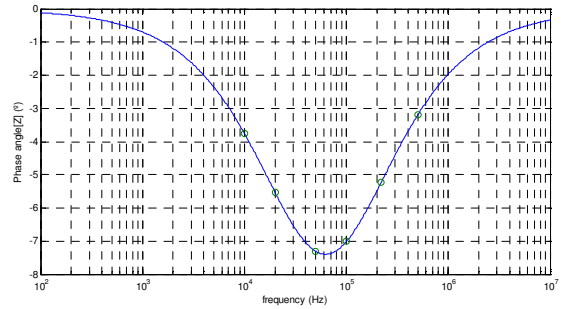


Fig. 4. Phase angle as function of frequency.

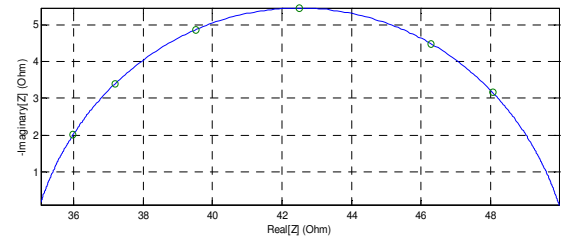


Fig. 5. Bioimpedance in the complex plane.

The ECW resistance (R_e) is equal to the extrapolated impedance at zero frequency (R_0) which becomes real. From the Cole-Cole model the impedance at infinite frequency R_{∞} is also extrapolated. (R_{∞}) is also real and represents the total body water resistance. (R_i) defined as the ICW resistance can be calculated from (R_0, R_{∞}) assuming (R_i) and (R_e) are in parallel. Fig.6.

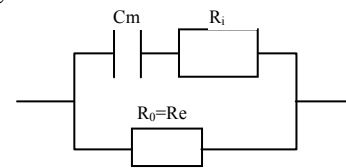


Fig. 6. Equivalent circuit model for the extracellular, intracellular and cell membrane spaces.

B. Estimating fluid volumes from bioimpedance data

The impedance of a cylindrical shaped object is:

$$Z = \rho \frac{L^2}{V} \quad (3)$$

Where:

Z : impedance in (Ohm)

L : length of the cylinder in (cm)

V : Volume of the cylinder in (cm^3)

ρ : Resistivity in (ohm.cm)

In bioimpedance measurements, L is assumed to be the separation distance between the detection electrodes and V is the volume to be estimated. However biological tissues are not homogenous; in fact they are considered as a suspension of conduction and non conducting materials. The apparent resistivity of suspensions can be calculated by Hanai mixture

theory (Eq.4) Hanai (1968) describes the apparent resistivity (ρ) of a mixture containing a nonconductive material with volumetric concentration (C) in a conducting media with resistivity (ρ_0) [8]

$$\rho = \frac{\rho_0}{(1-C)^{3/2}} \quad (4)$$

At low frequency ECW is considered as the conduction material, and ICW which is surrounded by cell membrane is the non conducting material .The volumetric concentration in Eq.3 can be written as :

$$C_{LF} = 1 - \frac{V_{ECW}}{V_{TTV}} \quad (5)$$

Where V_{TTV} is the total tissue volume.

At high frequency, the injected current will penetrate both ECW and ICW spaces, therefore we can write:

$$C_{HF} = 1 - \frac{V_{ECW} + V_{ICW}}{V_{TTV}} \quad (6)$$

The impedance at zero frequency, Z_0 is extrapolated form Cole mathematical model. Z_0 is real and describes the resistance of the ECW i.e ($Z_0=R_E$)

Using the basic impedance Eq.1 and using the volumetric concentration at LF Eq.5, the volume of the ECW can be calculated by:

$$V_{ECW} = \left(\frac{\rho_{ECW} L^2 V_{TTV}^{1/2}}{R_0} \right)^{2/3} \quad (7)$$

Using the extrapolated values of R_0 , R_∞ and the volumetric concentration at HF Eq.6, the volume of the ICW compartment can be calculated by:

$$\left(1 + \frac{V_{ICW}}{V_{ECW}} \right)^{5/2} = \frac{R_0}{R_\infty} \left(1 + K_P \frac{V_{ICW}}{V_{ECW}} \right) \quad (8)$$

Where

$$K_P = \frac{\rho_{ICW}}{\rho_{ECW}} \quad (9)$$

and ρ_{ECW} , ρ_{ICW} are the resistivity of the ECW,ICW in (Ohm.cm) respectively which can be found in literature.

II. METHODOLOGY

A. Bioimpedance sensor

The main objective of this work is to develop a non-invasive method based on local multifrequency bioimpedance measurements that allow us to determine the fluid distribution and variations during haemodialysis. For this purpose a measurement system was developed by our research group [9]. Fig.7

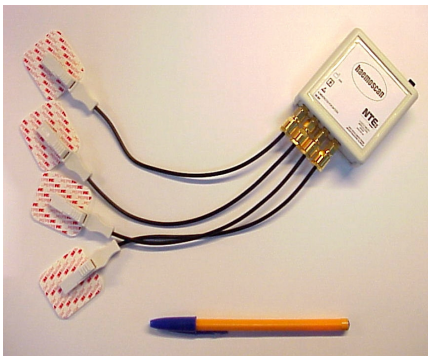


Fig. 7. Bioimpedance sensor developed at our research lab (UPC/Spain).

The main specifications of this bioimpedance sensor are listed in Table.I.

TABLE .I
SPECIFICATIONS OF THIS BIOIMPEDANCE SENSOR

Characteristic	Value
Measurement range of module	$5(\Omega) \leq Z \leq 200(\Omega) \pm 2.0\%$
Measurement range of phase	$0.5(\text{deg}) \leq \phi \leq 90(\text{deg}) \pm 2.0\%$
Electrical current	650 μA
Frequency range	10 kHz-1MHz
Power type	Battery operated (low power) Li-Ion
Operating time	8 hr at SR=(1 meas / 4 min, 6 freq.)
Weight	Lightweight :140(g), including cables, connectors and electrodes
Dimensions	60 X 60 X 25(mm)
Cables	20(cm) coaxial
Electrodes	Surface electrodes (3M Red Dot (TM) Ag/AgCl 2560)
Measurement type	Local Tissue Impedance spectroscopy

B. Experimental protocol

Clinical measurements were done in the Nephrology department/Medical center Parc Tauli /Sabadell/Spain. In these clinical measurements 60 haemodialysis sessions were included with average duration of 4 hours for each HD. 9patients (3M,6F) participated in these clinical trails (6-8 HD session for each patient). The basic patient data are shown in Table.II.

TABLE. II
PATIENT DATA

Patient	Age (year)	Sex	Height (cm)	Dry Weight (kg)
1	33	F	165	60
2	46	F	159	67
3	77	F	151	66.5
4	45	F	157	50
5	55	M	182	73
6	51	F	162	59.5
7	81	M	165	81
8	46	F	152	56
9	53	M	173	90
10	42	F	151	64.5

For each patient, three impedance sensors were attached to the arm, abdomen, and leg. At each segment the separation between the voltage detection electrodes was 10cm, and the injection electrodes were placed 5cm away from the voltage electrodes. Local tissue impedance module and phase were continuously recorded with 6 frequencies (10,20,50,100,220,500 kHz) with SR of 1 meas/4min. Continuous measurements of the total blood volume change (ΔBV) and heamatocrit (Hct) were obtained by an optical HCT analyzer (Crit-Line System). Intra dialysis clinical parameters such as: arterial blood pressure, ultrafiltration rate, and ultrafiltration accumulated were recorded every 20 minutes.

III. RESULTS

A. Pre and Post-HD states

Fig.8 shows the impedance module recorded from the leg at 6 frequencies (10,20,50,100,220,500kHz) during the HD treatment session. To compare the variations in the

impedance between the beginning and the end of the HD session, the impedance module and phase are plotted in the frequency domain for the pre and post-HD states as shown in Fig.9 and 10. At both states the measured impedances are fitted into the Cole-Cole model and plotted in the complex plane in order to extrapolate the impedance values at zero and infinite frequencies Fig.11

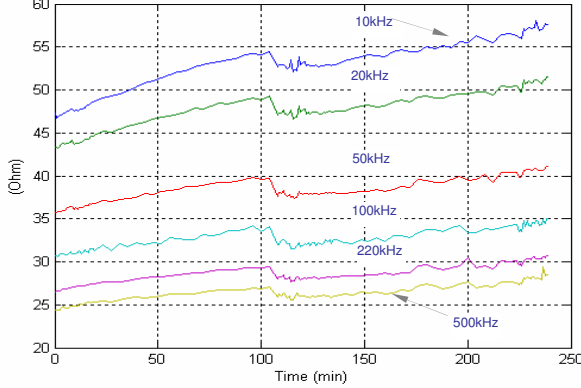


Fig.8. Bioimpedance Module recorded in the HD time.(Leg).

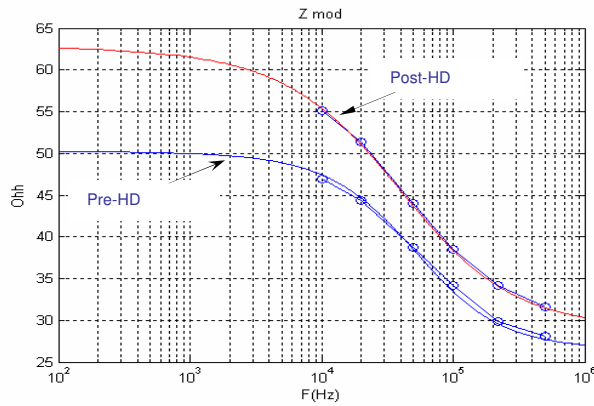


Fig.9. Bioimpedance Module .Pre-HD and post-HD in the frequency domain.

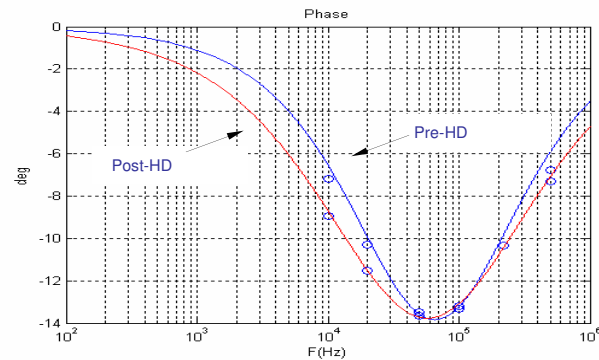


Fig. 10. Bioimpedance Phase .Pre-HD and post-HD in the frequency domain

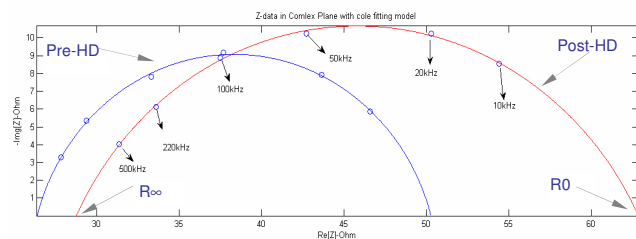


Fig. 11. Bioimpedance in the complex plane at the pre-HD and post-HD. Measured points (dots) and the fitting Cole-Cole model (solid line).

Total tissue volume (TTV) is estimated by measuring the circumferences and the separation between the detection electrodes. TTV decreases during HD the reduction percentage of the TTV is assumed to be equal to the total reduction of the body volume produced by the total ultrafiltration volume. For the pre and post-HD states the ECW and ICW volumes are estimated using the extrapolated values of R_0 and R_∞ as explained in Eq.7 and 8. Total tissue water (TTW) is defined as the summation of ECW and ICW volumes. The average values of the 6 HD sessions of each patient at pre and post-HD are listed in Table.III and IV.

TABLE. III
ESTIMATED VOLUMES FOR THE PRE AND POST-HD IN (cm³)

Patient	TTV(0)	TTV(f)	ECW(0)	ECW(f)	ICW(0)	ICW(f)	TTW(0)	TTW(f)
1	685.63	641.32	150.79	118.24	304.28	349.55	454.97	426.26
2	857.28	837.76	177.89	147.77	432.32	447.60	610.22	576.30
3	599.81	574.96	125.35	103.70	205.75	193.34	330.99	273.14
4	468.73	449.17	114.19	93.99	187.08	186.11	301.28	261.39
5	752.73	722.31	121.04	93.56	190.72	179.14	311.72	243.48
6	586.78	555.24	115.53	86.84	163.44	161.59	278.98	218.61
7	656.71	643.24	125.11	111.14	246.01	242.59	371.12	340.55
8	466.86	434.54	102.44	80.65	233.68	225.51	336.12	276.09
9	477.38	459.81	97.87	80.21	157.51	165.62	255.38	228.93

TABLE. IV
ESTIMATED VOLUMES FOR THE PRE AND POST-HD IN (cm³)

Patient	%ECW(0) TTW(0)	%ECW(f) TTW(f)	%ICW(0) TTW(0)	%ICW(f) TTW(f)	%ECW(0) TTV	%ECW(f) TTV	%ICW(0) TTV	%ICW(f) TTV	%UF = (UUF / Dry wt)
1	34.08	30.22	65.94	80.21	22.20	18.73	43.54	52.80	6.20
2	29.43	25.94	70.57	77.40	20.78	17.69	50.22	53.22	2.17
3	37.82	37.95	62.21	70.82	21.52	18.46	35.25	34.70	3.98
4	37.88	35.96	62.12	71.19	24.40	20.96	40.14	41.55	3.94
5	38.81	38.43	61.21	73.54	16.08	12.95	25.33	24.79	3.85
6	41.49	39.81	58.51	73.94	20.17	16.01	28.57	29.89	5.19
7	34.20	32.95	65.80	70.98	19.14	17.33	37.26	37.53	1.97
8	30.47	29.29	69.53	81.65	22.01	18.55	50.20	52.16	6.58
9	38.28	35.25	61.72	72.10	20.43	17.38	33.08	36.27	3.50

B. Continuous estimation of ECW and ICW during HD

For continuous monitoring of the variations in ECW and ICW during HD session, the same procedure explained previously is repeated at each point of the measurements instead of the beginning and end state of HD only.

Fig.12 shows the impedance in the complex plane and the Cole-Cole fitting for all the points from pre to post HD.

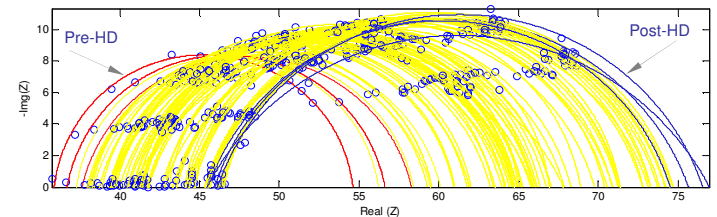


Fig. 12. Continuous representation of the Bioimpedance in the complex. Measured points (dots) and the fitting Cole-Cole model (solid line).

Relative changes in the ECW and ICW are calculated by:

$$C_{ECW}(\%) = 100 \frac{ECW(t) - ECW(t=0)}{ECW(t=0)} \quad (10)$$

$$C_{ICW}(\%) = 100 \frac{ICW(t) - ICW(t=0)}{ICW(t=0)} \quad (11)$$

Fluid balance is defined as

$$FB = \frac{ICW}{ECW} \quad (12)$$

And the relative change in FB is calculated by :

$$C_{\frac{ICW}{ECW}}(\%) = 100 \frac{\frac{ICW}{ECW}(t) - \frac{ICW}{ECW}(t=0)}{\frac{ICW}{ECW}(t=0)} \quad (13)$$

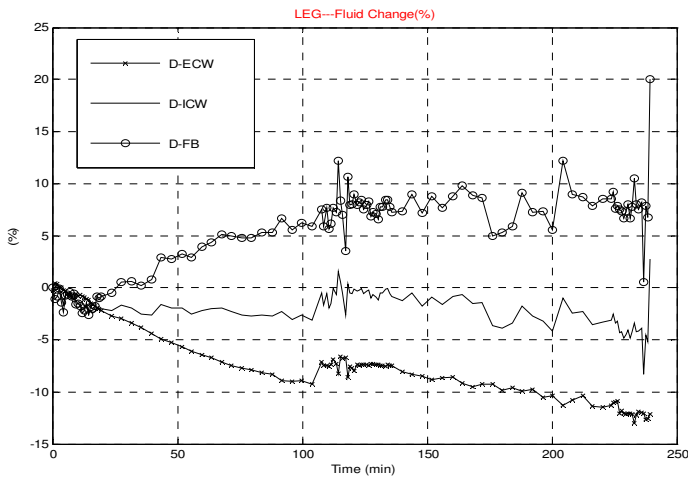


Fig.13. Relative changes (%) for the ECW, ICW and fluid balance during the HD session.

IV. DISCUSSION

Bioimpedance spectroscopy (BIS) is used to evaluate the volumes of the ECW and ICW compartments. This approach includes the injection of electrical current normally below 1(mA) at a range of frequencies. The questions that emerge here are: 'what is this frequency range? How low and high frequency is needed? and how many frequency points?'

The answer to these questions is : In order to evaluate the volumes of ECW and ICW we need to inject the electrical current in a range that goes as low as few (Hz) and as high as few M(Hz) with as many very high frequency samples as possible. However it is clear that this is impossible due to technical and health safety reasons especially in clinical applications. Instead, bioimpedance is measured at a selected frequency range and number of points and fitted into a mathematical model in order to extrapolate the impedance values at zero and infinite frequencies.

In this work the bioimpedance spectroscopy (BIS) method is proposed to estimate ECW and ICW volumes using a self designed BIS sensor during HD treatment sessions using 6 frequencies (10,20,50,100,220,500 kHz). Results show a significant decrease in the measured impedance during HD induced by water removal via ultrafiltration Fig.8. The Cole-Cole model was able to fit the measurement points at the 6 selected frequencies with high accuracy as shown in Fig.9-11 and the values of R_0 and R_∞ were extrapolated with high confidence.

The total relative changes in the estimated total tissue water (TTW) and intracellular water (ECW) showed a significant decrease between the pre and post-HD for all patients as shown in Table.III and Fig.14.

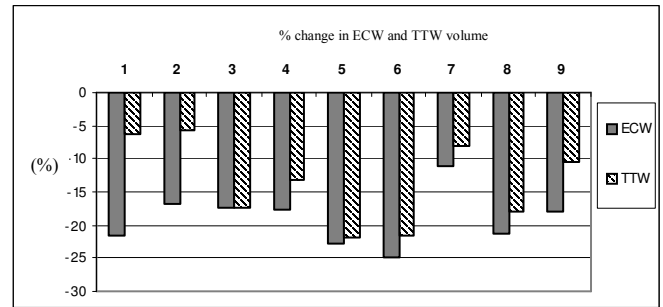


Fig.14. Total relative changes (%) for the ECW and TTW after the HD session.

The estimated intracellular volume (ICW) did not show a constant decreasing behavior as recorded in ECW and TTW as shown in Table.III and Fig.15.

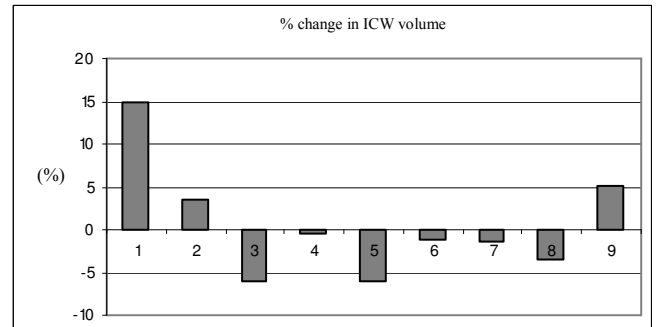


Fig.15. Total relative changes (%) for the ICW after the HD session.

The ECW ratio to the total tissue volume (ECW/TTV) and the ECW ratio to the total tissue water (ECW/TTW) were evaluated for the pre and post-HD states. The same was done for the ICW. A clear decrease in the ECW ratios were always recorded between the pre and post-HD states, however an increase was mostly recorded for the ICW ratios as shown in Table.IV and Fig.16-17. This can be explained by the fact that ultrafiltration involves water removal which mostly comes from ECW space pace.

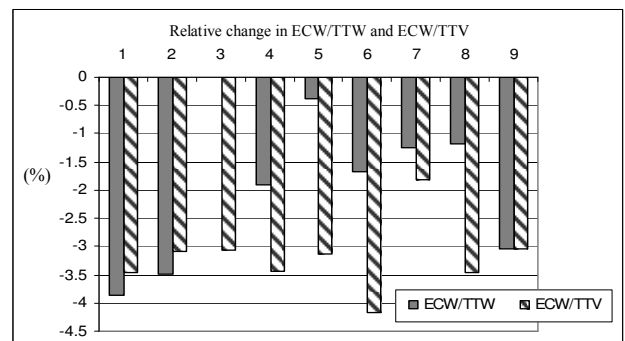


Fig.16. Total relative changes in ECW/TTW and ECW/TTV after the HD session.

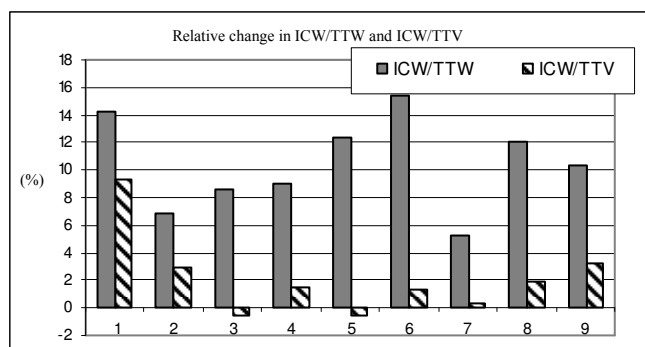


Fig.17. Total relative changes in ICW/TTW and ICW/TTV after the HD session.

V. CONCLUSIONS

Bioimpedance spectroscopy method was used to estimate the ECW, ICW and TTW volumes for patients during haemodialysis treatment sessions using 6 frequencies. The Cole-Cole mathematical model was used to fit the measured points in order to extrapolate the impedance values at zero and infinite frequencies. Precise matching was recorded between the measured points and the fitting model which indicate an accurate impedance sensor in the measurement frequency range. ECW and TTW volumes and the ratios ECW/TTW ECW/TTW showed a clear decrease in response to ultrafiltration during HD in all patients. However the behavior of ICW volume variation was not the same in all patients. The ratios ICW/TTW and ICW/TTV showed an increase between the pre and post-HD states which indicates that water is removed more from the extracellular space during ultrafiltration.

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